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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,926	11/13/2003	Pavel Slanina	SYN-0036	7713

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SYNTHON IP INC
7130 HERITAGE VILLAGE PLAZA
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GAINESVILLE, VA 20155

EXAMINER

MOORE, SUSANNA

ART UNIT	PAPER NUMBER
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1624

MAIL DATE	DELIVERY MODE
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09/27/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	Application No. 10/705,926	Applicant(s) SLANINA ET AL.	
	Examiner Susanna Moore	Art Unit 1624	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 September 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 9/4/2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) ☐ They raise the issue of new matter (see NOTE below);
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
 5. ☒ Applicant's reply has overcome the following rejection(s): _____.
 6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
 The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: _____.
 Claim(s) objected to: 12.
 Claim(s) rejected: 1-9 and 13.
 Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
 10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
 13. ☐ Other: _____.

DETAILED ACTION

The period for reply continues to run SIX MONTHS from the date of the final rejection. Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a) accompanied by the appropriate fee. The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. A reply within the meaning of 37 CFR 1.113 or a request for a continued examination (RCE) in compliance with 37 CFR 1.114 must be timely filed to avoid abandonment of this application.

The amendment filed September 4, 2007 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance but will be entered because: the proposed amendment is deemed to place the application in better form for appeal by materially simplifying the issues for appeal.

The Rule 1.132 declaration submitted by Martin Dobsik has overcome the 102 (b) art rejections made with the Kennis reference (U.S. 4804663).

Claim Rejections - 35 USC § 102

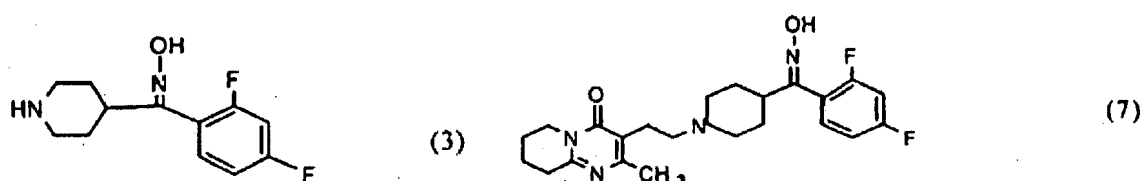
Claims 9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Marquillas Olondriz et. al. (ES 2050069).

Marquillas Olondriz et. al. teaches the reaction of the oxime intermediate 7 to the cyclized product, risperidone, with sodium in refluxing THF. See column 6, example 9, lines 60-

67, and column 7, lines 1-28, and the final cyclized product, column 7, example 10, lines 30-47 and column 8, lines 1-15.

In addition, Marquillas Olondriz et. al. must have had the oxime enriched with the Z-isomer to obtain a yield of 87.7% of the cyclized product. Applicant discloses on page 7 of the Specification that the E-isomer is "unreactive" due to the orientation of the hydroxyl group pointing away from the fluoro substituent. Thus, the Z-isomer must have been present in the oxime mixture in excess of 90%, since most cyclized reactions do not go to 100% yield.

The rejected claims are drawn to the enriched Z-isomer oxime 7 in greater than 80% yield.



The Specification on page 10 states, "An enriched Z-isomer oxime of formula (3) and (7) can also be obtained by conversion of the E-isomer oxime into the Z-isomer form. Specifically, by heating the E-isomer, typically a mixture of the Z- and E-isomers, in a solvent, the E-isomer is converted into the Z-isomer. More specifically, the undesired E-isomer is converted into the E-isomer of the oxime...by heating in an inert solvent...at a sufficient temperature, preferably, higher than 80°C."

The Specification also states on page 7, "Because of the discovery that the E-isomer oxime is not merely slower reacting than the Z-isomer oxime but rather is essentially unreactive,...."

As the Specification says the enrichment occurs on "heating in an inert solvent," this heating inherently produces the enrichment.

Applicant traverses the above rejection by stating, "Thus, Olondriz's 84.7% yield does not necessarily require an initially high isomeric putty, as the Office Action contends, but could simply be the result of equilibrium forces surrounding the isomerisation and cyclization of the Z-isomer." Indeed, Applicant may be correct about the isomerization occurring during the reaction. However, the Specification, on page 10, states, "More specifically, the undesired E-isomer of the oxime of formula (3) may be isomerised to the Z- isomer by heating it in an inert solvent, such as, n-butanol, at a sufficient temperature, preferably, higher than 80°C. Furthermore, the heating process may be carried out faster in the presence of an acid catalyst... For example, heating essentially pure E-isomer of the oxime of formula (7) in n-butanol with 5 equivalents of acetic acid at 100°C, a 70% conversion is obtained after 12 hours." The reference teaches the reaction conditions in refluxing THF, which boils at approximately 68° C, for one hour and without a catalyst. Furthermore, even if the Z isomer was only present in 95% purity, the amended percent in claim 9, and the reaction went to 90% yield, this would provide an overall reaction yield of 85.5%, which is very close to the yield obtained in the reference, 84.7%. Moreover, the Examiner has produced a *prima facie* case to meet its burden.

Thus, the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strupczewski et. al. (U.S. 4,408,054).

The current invention teaches the process of making and use of acetic acid salts of oximes (3) and (7).

Strupczewski et. al. teaches compounds of salts of oxime (3). The compound 4-(2,4-difluorobenzoyl)-piperidine oxime is used in example 25, column 26, lines 66-67. This oxime intermediate is used for the exact same utility, the cyclization to the corresponding benzoisoxazole.

The difference between the prior art and the current invention is that the prior art reference uses the free base of compound (3) while Applicant uses the acetic acid salt of compound (3).

Claim 1 of the prior art references claims the oxime (3) "or salts thereof." See paragraph bridging columns 38 and 39. The only definition of salts is found in column 10, lines 61-68 of the patent, which lists 9 different pharmaceutically acceptable salts. Acetic acid is one of the salts mentioned, and therefore, acetic acid would be an obvious choice to use for compound (3).

The compound, 4-(2,4-difluorobenzoyl)-piperidine oxime, is used for the same utility in the reference as in the current invention, the synthesis of risperidone. The same sequence of reactions occurs, where the oxime is cyclized intramolecularly to the benzoisothiazole in refluxing water as the solvent. See column 27, lines 16-39. This heating does the enrichment.

The inherency argument mentioned above applies here as well. Thus, claims 1-8 are obvious over the teachings of Strupczewski et. al.

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Applicant argues that the "salts thereof" only corresponds to the final cyclized products, the benzoisoxazoles. As mentioned previously, this is not true. The referenced patent in claim 1, claims compounds of formula (3) and salts thereof. These salts are not limited only to the final products. The disclosure in column 10, lines 64, recites acetic acid as one of the preferred pharmaceutically acceptable additions salts. Since this is the only teaching of salts disclosed by the reference, one of ordinary skill in the art would use this list as a guide.

Thus, the rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

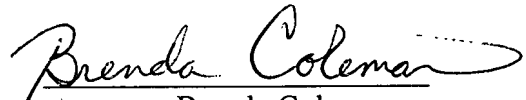
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


SM

9/18/07



Brenda Coleman
Primary examiner
Art Unit 1624
Technology Center 1600